L^1 is -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^5)$-, -$CON(R^5)$-, -$OC(O)N(R^5)$-, -$CSN(R^5)$-, -$N(R^5)CO$-, -$N(R^5)C(O)O$-, -$N(R^5)CS$-, -$S(O)N(R^5)$-, -$S(O)_2N(R^5)$-, -$N(R^5)S(O)$-, -$N(R^5)S(O)_2$-, -$N(R^5)CON(R^5)$-, -$N(R^5)CSN(R^5)$-, -$N(R^5)SON(R^5)$-, or -$N(R^5)SO_2N(R^5)$-;

r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R^1 is an optionally substituted pyridyl group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from -$N(R^3)CO$-, (where R^3 is a hydrogen atom or a straight or branched alkyl group); -$N(R^3)SO_2$-, -$N(R^3)C(O)O$- or -$N(R^3)CON(R^{3a})$- (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, or C_{7-10}tricycloalkenyl group;

and the salts, solvates, hydrates and N-oxides thereof.

18. (Amended) A method for inhibiting the binding of α4 integrins to the ligands thereof in a mammal suffering from a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role, comprising administering to the mammal an effective amount of a compound according to Claim 1.

REMARKS

Claims 1 and 5 to 19 are pending in the application. Claims 1, 14, and 18 have been amended herein. No new claims have been added, and no claims have been cancelled.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Preliminarily, Applicants acknowledge with appreciation the Examiner's indication that certain of the rejections have been withdrawn.

I. Alleged Lack of Enablement

A. Claim 15 has been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully traverse the rejection because the Office Action has failed to meet its burden of establishing a reasonable basis to question the enablement provided in the specification for the subject matter defined by claim 15.

When making an enablement rejection, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971). Acceptable support for an enablement rejection can take the form of ***specific findings of fact, supported by the evidence***. M.P.E.P. § 2164.04 (emphasis added). "References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 24 (C.C.P.A. 1971). However, ***specific technical reasons are always required***." M.P.E.P. § 2164.04 (emphasis added).

Applicants respectfully submit that the Office Action has failed to meet its burden in establishing that the subject matter defined by claim 15 is not enabled by the specification.

As discussed in the Request for Reconsideration filed May 15, 2002, the specification enables those of ordinary skill in the art to practice the full scope of the subject matter defined by the claims without undue experimentation. The specification provides abundant guidance regarding how to synthesize the compounds defined by the present claims and how to quantify their potency as integrin inhibitors. In addition, the specification teaches those of ordinary skill in the art how to formulate pharmaceutical compositions containing the claimed compounds and how to administer such compositions for the prophylaxis or treatment of the recited diseases and disorders. The Office Action has failed to provide any credible evidence or reasoning as to why the truth or accuracy of the direction provided in the specification should be doubted, and, therefore, has failed to establish lack of enablement of the subject matter defined by claim 15.

It is respectfully submitted that the present Office Action failed to respond to Applicants' arguments and evidence provided in the Request for Reconsideration filed May 15, 2002, and merely repeated conclusory statements regarding alleged lack of enablement that had been made in the previous Office Action. The Office Action states that the fifth, sixth, seventh, and eighth Wands factors have not been satisfied, but offers no findings of fact or evidence in support of its assertions. The Office Action further states that "[u]ndue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor." Office Action dated August 19, 2002, page 3. The Office Action has failed to explain why it doubts the truth or accuracy of the statements made in the specification, and has failed to support its assertions with specific findings of fact, evidence, references, or specific technical reasons. Notably, the Office Action has offered no evidence that establishes unpredictability in the art.

As discussed above, in the Office Action dated December 21, 2001, statements identical to those made in the present Office Action (dated August 19, 2002) were made in support of the rejection of claim 15 for alleged lack of enablement. In the Office Action dated April 26, 2001, the only statement made in support of the rejection of claim 15 for lack of enablement was that "[t]here is no known cure in the art for multiple sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement." Office Action dated April 26, 2001, page 4. Again, the Office Action failed to explain why it doubts the truth or accuracy of the statements made in the specification, and failed to support its assertions with specific findings of fact, evidence, references, or specific technical reasons.

With respect to the assertion made in the Office Action dated April 26, 2001 that "[t]here is no known cure in the art for multiple sclerosis," as Applicants explained in the Request for Reconsideration filed May 15, 2002, claim 15 does not recite a method for *curing* multiple sclerosis, but, rather, recites a method for the *prophylaxis or treatment* of, *inter alia*, multiple sclerosis. Applicants directed the Examiner to the attached Drug Report (resubmitted herewith as Appendix A) describing a humanized monoclonal antibody that acts as a specific inhibitor of the $\alpha 4\beta 1$ integrin VLA4, which is currently in Phase III clinical trials for the treatment of multiple sclerosis. In addition, Applicants also direct the Examiner to the attached chapters from Cell Adhesion Molecules and Matrix Proteins – Role in Health and Diseases, S.A. Mouse (editor), Springer, 1998 ("the Mouse excerpt")(enclosed herewith as Appendix B). The Mouse excerpt indicates that inhibition of VLA4 in animal models of multiple sclerosis (known as experimental autoimmune encephalomyelitis or EAE) using anti-$\alpha 4$ integrin monoclonal antibodies is effective in attenuating signs of paralysis and

suppressing mononuclear cell infiltration into CNS tissue. See chapter 8, pages 140 to 142. Alpha4 integrin inhibitors have therefore been shown to be effective for the treatment of multiple sclerosis in animal models and in clinical studies performed on humans. In contrast to the assertion made in the Office Action, cell adhesion inhibitors, specifically α4 integrin inhibitors, ***are*** recognized in the art as efficacious for the treatment of multiple sclerosis.

The Office Action has failed to meet its burden of establishing a reasonable basis to question the enablement provided in the specification for the subject matter defined by claim 15. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Claims 1, 5 to 11, and 14 to 19 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully traverse the rejection because the Office Action has failed to meet its burden of establishing a reasonable basis to question the enablement provided in the specification for the subject matter defined by the cited claims.

As discussed above, the specification enables those of ordinary skill in the art to practice the full scope of the subject matter defined by the claims without undue experimentation. The Office Action has failed to provide any credible evidence or reasoning as to why the truth or accuracy of the direction provided in the specification should be doubted, and, therefore, has failed to establish lack of enablement of the subject matter defined by the claims.

The Office Action asserts that "the specification does not reasonably provide enablement for Alk1 in the compound of formula (1a) equaling C1-6 heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups." Office Action dated August 19, 2002, page 4. The Office Action, however, has failed to provide any explanation whatsoever as to ***why*** the specification is not enabling for the cited compounds of

formula 1a, much less provide support for its assertions with specific findings of fact, evidence, references, or specific technical reasons. As discussed below, without conceding the correctness of the rejection, claims 1 and 14 have been amended to recite particular heteroatoms and heteratom-containing groups defined by Alk^1. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

The Office Action also asserts that "the specification does not reasonably provide enablement for...R4 equal to C3-10 cycloaliphatic or C7-10 polycycloaliphatic groups." Office Action dated August 19, 2002, page 4. Again, the Office Action has failed to offer any explanation as to why the specification is not enabling for the cited compounds of formula 1a, and has failed to meet its burden in establishing lack of enablement. Nevertheless, in an effort to advance prosecution, claims 1 and 14 have been amended to replace C_{3-10} cycloaliphatic with "C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl" and to replace C_{7-10} polycycloaliphatic with "C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, and C_{7-10}tricycloalkenyl." Support for the amendments is found in the specification at, for example, page 10, lines 8 to 24. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

The Office Action also asserts that "the specification does not enable the treatment of all diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role in a mammal with these compounds." Office Action dated August 19, 2002, page 4. The Office Action has merely offered conclusory statements in support of this assertion, and has failed to provide support for its assertions with specific findings of fact, evidence, references, or specific technical reasons. For example, the Office Action makes conslusory statements about the breadth of the claims, stating that "Alk1 of the compound of formula (1a) also encompasses a broad breadth C1-6 heteroaliphatic chain containing one,

two, three or four heteroatoms or heteroatom-containing groups." As discussed previously, and below, claims 1 and 14 have been amended to recite particular heteroatoms and heteratom-containing groups defined by Alk[1]. The Office Action further states that "the level of predictability in the art is low and the amount of direction provided by the inventor is low since the applicant does not specify the test results for each of the tests compounds. The applicant also does not test these compounds effects on actual specified diseases." The Office Action, however, has failed to establish the level of predictability in the art, and has failed to offer any evidence that the level of predictability in the art is low. Furthermore, it is well established that Applicants are not required to provide test data for every species encompassed by a claim. *In re Angstadt*, 537 F.2d 498, 502-503 (C.C.P.A. 1976). Moreover, the Office Action has failed to offer any credible evidence or reasoning as to why the truth or accuracy of the direction provided in the specification should be doubted.

The Office Action further asserts that "undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor." Again, the Office Action has merely offered conclusory statements in support of its assertion of non-enablement, and has failed to support its assertions with specific findings of fact, evidence, references, or specific technical reasons. Accordingly, Applicants respectfully request withdrawal of the rejection.

Finally, the Office Action asserts, with respect to claims 18 and 19, that the diseases being treated by the inhibition of $\alpha 4$ integrins are not recited in the claims, and "the inhibition of an enzyme must be related to a disease that needs to be improved and this disease needs to be recited." Office Action dated August 19, 2002, page 5. Without conceding the correctness of the assertion, and to advance prosecution, claim 18 has been amended to recite

"a method for inhibiting the binding of α4 integrins to the ligands thereof in a mammal suffering from a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role..." Support for the amendment is found in the specification at, for example, page 3, lines 25 to 32 and page 4, line 31 to page 5, line 8. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

II. Alleged Indefiniteness

A. Claims 1 and 14 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite because the phrase "C_{1-6}heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups" allegedly makes it unclear as to which heteroatoms are being claimed and whether the heteroatoms are the same or different. Applicants respectfully submit that the meaning of the cited phrase would be readily understood by those of ordinary skill in the art. Nevertheless, to advance prosecution, claims 1 and 14 have been amended to recite particular heteroatoms. Support for the amendments is found in the specification at, for example, page 9, lines 6 to 12 and page 8, lines 18 to 26. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

B. Claims 1, 12, and 14 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase "salts, solvates, hydrates and N-oxides thereof." Applicants respectfully traverse the rejection because the cited phrase conveys a clear and definite meaning to those of skill in the art.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112

[second paragraph] demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). If a skilled artisan can determine whether a particular chemical compound is or is not within the scope of a claim, the requirement of § 112, second paragraph has been fulfilled. *In re Miller*, 441 F.2d 689, 692 (C.C.P.A. 1971).

Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971); M.P.E.P. § 2173.02. When the present claim language is so examined, it becomes apparent that the meaning of the phrase "salts, solvates, hydrates, and N-oxides thereof" would be readily understood by those of ordinary skill in the art.

The Office Action asserts that the cited phrase is indefinite because Applicants claim "a compound," which is one compound, while the cited phrase implies that more than one compound is being claimed. Office Action dated August 19, 2002, pages 6 to 7. Applicants respectfully submit that those of ordinary skill in the art recognize that Applicants' claims cover numerous compounds. In fact, according to established principles of claim construction, Applicants are claiming every compound that falls within the scope of the claims. Consequently, those of ordinary skill in the art would readily understand the phrase "salts, solvates, hydrates and N-oxides thereof" to describe the salts, solvates, hydrates and N-oxides of any compound falling within the scope of the claims. Accordingly, the phrase conveys a clear and definite meaning to those of skill in the art, which allows the scope of the claims to be readily ascertained. The requirements of the second paragraph of § 112 have therefore been met, and Applicants respectfully request withdrawal of the rejection.

Information Disclosure Statements

Numerous Information Disclosure Statements, accompanying 1449 Forms, and references listed on the 1499 Forms, have been submitted to the Patent Office throughout the course of prosecution of the present application. The majority of the 1449 Forms have not been initialed by the Examiner and returned to Applicants. The present Office Action and previous Office Actions state that the Examiner has not received copies of the references listed on the 1449 Forms. Applicants have received date-stamped return post cards indicating that ***all*** of the references that have been submitted in connection with Information Disclosure Statements filed for the present application have been received by the Patent Office. A separate Communication in which numerous 1449 Forms and the references cited therein are being resubmitted to the Patent Office will be delivered directly to the Examiner to address this issue.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Jane Inglese

Date: December 17, 2002

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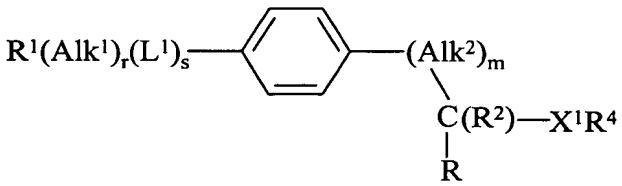
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 14, and 18 have been amended as follows.

1. (Amended Four Times) A compound of formula (1a):



wherein:

R is a carboxylic acid;

R^1 is an optionally substituted pyridyl group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or an optionally substituted C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups selected from the group consisting of -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, and $-N(R^5)SO_2N(R^5)-$;

R^5 is a hydrogen atom or a straight or branched alkyl group;

L^1 is -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, or $-N(R^5)SO_2N(R^5)-$;

~~R^5 is a hydrogen atom or a straight or branched alkyl group;~~

r and s, which may be the same or different, is each zero or an integer 1;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

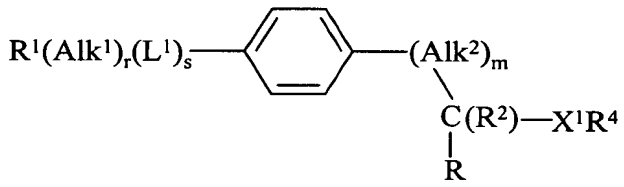
R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or branched alkyl group); $-N(R^3)SO_2-$, $-N(R^3)C(O)O-$ or $-N(R^3)CON(R^{3a})-$ (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, ~~C_{3-10} cycloaliphatic~~ C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, ~~or C_{7-10} polycycloaliphatic~~ C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, or C_{7-10}tricycloalkenyl group;

and the salts, solvates, hydrates and N-oxides thereof.

14. (Amended Three Times) A method for the prophylaxis or treatment of a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role in a mammal, which comprises administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound of formula (1):



wherein:

R is a carboxylic acid (CO_2H);

R^1 is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted pyridyl group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or an optionally substituted C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups selected from the group consisting of -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, and $-N(R^5)SO_2N(R^5)-$;

R^5 is a hydrogen atom or a straight or branched alkyl group;

L^1 is -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, or $-N(R^5)SO_2N(R^5)-$;

~~R^5 is a hydrogen atom or a straight or branched alkyl group;~~

r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R^1 is an optionally substituted pyridyl group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or branched alkyl group); $-N(R^3)SO_2-$, $-N(R^3)C(O)O-$ or $-N(R^3)CON(R^{3a})-$ (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, ~~C_{3-10} cycloaliphatic~~ C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, ~~or C_{7-10} polycycloaliphatic~~ C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, or C_{7-10}tricycloalkenyl group;

and the salts, solvates, hydrates and N-oxides thereof.

18. (Amended) A method for inhibiting the binding of α4 integrins to the ligands thereof in a mammal suffering from a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role ~~A method for inhibiting, in a mammal, the binding of α4 integrins to the ligands thereof~~, comprising administering to the mammal an effective amount of a compound according to Claim 1.